REMARKS

These remarks are in response to Office communication mailed August 17, 2007, and further in response to the Office Action dated January 30, 2007. By the present communication, no claims have been added, claim 4 has been canceled without prejudice, and claims 1, 2, 5 and 11 have been amended to define Applicant's invention with greater particularity. Support for the amended claims may be found in the specification as filed. As such, the amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Accordingly, upon entry of the present amendment, claims 1-3, 5-6, 8-13, and 15 will be under consideration.

Restriction Requirement

Applicant affirms the election of the species of S100 proteins in the reply filed on July 25, 2006, and further affirms the election of the species TRAF2 during the telephone conference with the Examiner on January 8, 2007.

Claim Objections

Applicant respectfully traverses the objection of claim 2 as allegedly containing an improper Markush group. To the extent that claim 2 is deemed canceled as a result of the response filed June 1, 2007, Applicants respectfully request reinstatement of claim 2. Without acquiescing to the reasoning offered by the Office Action, and in order to expedite prosecution of the instant application, Applicant has amended claim 2 to correct the Markush group. Withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. §112, First Paragraph

Applicant respectfully traverses the rejection of claims 1-6 and 8-10 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Office Action alleges that the specification fails to provide an adequate written description for the full breadth of the claimed inhibitors of production of S100 proteins. Applicant has canceled claim 4, rendering the rejection moot as to that claim. Without acquiescing to the reasoning offered by the Office Action, and in order to expedite prosecution of the instant application, Applicant has amended claim 1 to limit the claimed inhibitors to A20 and NG-monomethyl-L-arginine acetate (NMMA). Support for the amended claim language may be found, among others at, paragraphs [0035] and [0036] of the specification (A20), and at paragraphs [0110] and [0111] of the specification (NMMA). Further support may be found at paragraph [0041] of the specification as filed. Accordingly, Applicant respectfully submits that the specification provides an adequate written description for the full scope of the amended claims, and requests withdrawal of the rejection.

Applicant respectfully traverses the rejection of claims 1-6 and 8-10 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement. Specifically, the Office Action alleges that although the specification is enabling for methods that recite A20, it does not reasonably provide enablement for methods that recite any blocking agent. As discussed above, without acquiescing to the reasoning offered by the Office Action, and in order to expedite prosecution of the instant application, Applicant has amended claim 1 to limit the claimed inhibitors to A20 and NG-monomethyl-L-arginine acetate (NMMA). Support for the amended claim language may be found, among others at, paragraphs [0035] and [0036] of the specification (A20), and at paragraphs [0110] and [0111] of the specification (NMMA). Further support may be found at paragraph [0041] of the specification as filed.

Applicant further directs the Examiner's attention to the specification at paragraph [0094], wherein determination of the level of TGase activity *in vitro* is described. Applicant submits that the cited passage clearly illustrates methods which assess tTGase activity as a measure of matrix calcification. Further, paragraph [0098] describes methods to determine matrix calcification in response to the presence or absence of TGase and FXIIIa inhibitors. Paragraphs [0103]-[0109] also describe the expression and localization of FXIII and tTGase in normal versus abnormal knee cartilages, in essence, providing data which supports the correlation between inhibition of tTGase and FXIIIa and reduction of pathological calcification.

Accordingly, Applicant respectfully submits that the skilled artisan would be able to practice the full scope of the claimed invention without undue experimentation, and requests withdrawal of the rejection.

Rejections under 35 U.S.C. §112, Second Paragraph

Applicant respectfully traverses the rejection of claims 1-4 under 35 U.S.C. §112, second paragraph as being indefinite for allegedly failing to recite requisite steps necessary to practice the invention. Without acquiescing to the reasoning offered by the Office Action and in order to expedite prosecution of the instant application, Applicant has amended claim 1 to require contacting the cartilage matrix of a subject in need thereof with an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix. Applicant respectfully submits that the amended claims now recite the requisite patient population and the specific agents to be administered, and requests withdrawal of the rejection.

Rejections under 35 U.S.C. §103

Applicant respectfully traverses the rejection of claims 1, 2, 5 and 8-13 under 35 U.S.C. §103(a) as allegedly obvious over Nurminskaya et al. (hereinafter "Nurminskaya"), in view

Hashimoto et al.,(hereinafter "Hashimoto"). The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The Office Action alleges that Nurminskaya teaches that expression of transglutaminase (tTGase) and zymogen factor (FXIIIa) is unregulated in chondrocytes. The Action further alleges that this disregulation would have been obvious to lead one skilled in the art to the conclusion that blocking activation or activity of these factors would decrease apoptosis "in pathological states." However, the Action concedes that the reference does not specifically teach as such (Office Action, page 10, fist paragraph).

Applicant respectfully submits that the skilled artisan, on reading Nurminskaya in view of Hashimoto, would not ascertain that inhibiting transglutaminase (tTGase) and zymogen factor (FXIIIa) would result in effectively treating a pathological calcification in cartilage. In fact, Nurminskaya teaches away from the claimed invention in that the Nurminskaya's emphasis for the study of transglutaminase is focused on *plasma* transglutaminase and not *tissue* transglutaminase (tTGase). Applicant respectfully directs the Examiner's attention to page 1136, left side column, last paragraph, wherein the Nurminskaya states:

> The expression of two transglutaminases in hypertrophic chondrocytes – the *tissue form* (i.e., tTGase) that is constitutively active, and the plasma form that requires proteolytic activation –suggests that each may serve different roles. In the present study, we have begun to elucidate these functions in the avian growth cartilage, with emphasis on the enzymatically activated form (i.e., plasma transglutaminase) of factor XIIIA.

Applicant respectfully submits that Nurminskaya is directed at study of XIIIA and not at examining the significance of tTGase inhibition. More importantly, Nurminskaya clearly suggests that the role of tissue transglutaminase activation with regard to apoptotic cell death is of such little consequence that research efforts in this study were directed away from examination of this form of transglutaminase.

Applicants further submit that the level of unpredictability in the art in this area is such that the skilled artisan would not find that inhibition of tTGase and zymogen factor XIIIA is relevant in decreasing matrix calcification. The Examiner's attention is further directed to Nurminskaya at page 1141, second column, first paragraph under "Discussion," which discloses,

> we also have observed the mRNA for this form (i.e., tissue transglutaminase) of the enzyme to be upregulated in the hypertrophic zone of the avian growth region. Compared with the plasma form, however, this represents a small portion of overall transglutaminase activity produced by hypertrophic chondrocytes.

Applicant respectfully asserts that the reference provides no suggestion to arrive at the present invention because: 1) the research in Nurminskaya is focused solely at the role of *plasma* XIIIa in cellular apoptosis; 2) the role of tissue transglutaminase is so de-emphasized by the Nurminskaya's data that one skilled in the art would believe only *plasma* XIIIa to be critical in inhibiting cellular apoptosis; and 3) Nurminskaya's overall lack of discussion regarding inhibition of activation of FXIIIa and tTGase. It is also noted that Nurminskaya is directed at examination of cellular apoptosis, not suppressing meniscal and articular cartilage matrix as required by the claimed invention.

Applicant submits that the disclosure of Hashimoto fails to cure the above-described deficiencies in the primary reference, Nurminskaya. Hashimoto allegedly discloses that articular cartilage matrix calcification and degradation are implicated in human osteoarthritis. Hashimoto also allegedly discloses that "future treatment options" (*e.g.*, apoptotic inhibitors) would alleviate chondrocyte apoptosis. Applicant respectfully submits that the data presented in Hashimoto merely provides a generalized observation that increased chondrocyte apoptosis occurs in

osteoarthritis cartilage and is correlated with the severity of cartilage degradation. Furthermore, Hashimoto is absolutely silent with regard to any suggestion of using A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification in the cartilage matrix.

Accordingly, Applicant respectfully submits that one of ordinary skill in the art would not have been motivated to combine the disclosures of Nurminskaya and Hashimoto to arrive at the Applicant's invention. Even if one were motivated to combine the two references, Applicant submits that the skilled artisan would not arrive at the claimed methods of inhibiting tissue transglutaminase as well as zymogen Factor XIIIa. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Applicant respectfully traverses the rejection of claims 3, 4 and 6 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nurminskaya, in view of Hashimoto, and further in view of Heyninck et al., (herein after "Heyninck"). The remarks provided above above distinguishing the invention over the combined disclosures of Nurminskaya and Hashimoto apply equally and are incorporated here. The Office Action relies upon Heyninck for allegedly teaching that cellular expression of A20 inhibits TRAF2 mediated NF-kB signal transduction. Applicant has canceled claim 4 without prejudice, rendering the rejection moot as to that claim. Applicant respectfully submits that Heyninck is absolutely silent with regard to using A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification in the cartilage matrix, as required by the claimed invention.

Accordingly, even if one were to combine Nurminskaya with Hashimoto and Heyninck, the resulting combination would not be *prima facie* obvious over the claimed invention since the combined references do not disclose each and every claim limitation. Accordingly, withdrawal of the rejection is respectfully requested.

Applicant respectfully traverses the rejection of claim 15 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nurminskaya, in view of Hashimoto, and further in view of Studer, et al. (herein after "Studer"). The remarks provided above distinguishing the invention over the combined disclosures of Nurminskaya and Hashimoto apply equally and are incorporated here. The Office Action relies upon Studer for allegedly disclosing that inhibitors of NOS relieve the inhibition of cartilage matrix synthesis occurring in response to IL-1. The Office also alleges that Studer teaches that NO induces apoptosis in articular chondrocytes leading to eventual calcification in human osteoarthritis. Applicant respectfully submits that the Examiner has mistakenly concluded that Studer teaches that NO induces apoptosis, when in fact, Studer merely alleges that there "is evidence supporting that NO induces apoptosis...." (Studer, page 377, paragraph 2). Applicant respectfully asserts that contrary to the Examiner's conclusion regarding the reference, Studer does not teach that NO induces apoptosis in articular chondrocytes but rather discloses,

> we have recently transduced chondrocytes with iNOS (NOS-2) gene and confirmed the ability of the endogenously produced NO to inhibit matrix synthesis. Despite the high levels of NO made by these cells, there was *no* evidence of apoptosis or other forms of cell death. (Studer, Summary, page 377, emphasis added; see also page 378, third paragraph).

Applicant respectfully submits that one of skill in the art would be motivated, in view of Studer, to arrive at the claimed invention since the available data indicates that despite high levels of NO, apoptosis was *not* observed in iNOS transduced chondrocytes. Hence, given the high level of unpredictability in the art, it cannot be reasonably concluded that one of skill in the art would have contemplated using a NOS inhibitor, as required by claim 15, to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes of the cartilage matrix.

Accordingly, even if one were to combine Nurminskaya with Hashimoto and Studer, the resulting combination would not be *prima facie* obvious over the claimed invention since the

combined references do not disclose each and every claim limitation. Accordingly, withdrawal of the rejection is respectfully requested.

Applicant respectfully traverses the rejection of claim 2 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nurminskaya, in view of Hashimoto, and further in view of Gohr, et al (herein after "Gohr"). The remarks provided above distinguishing the invention over the combined disclosures of Nurminskaya and Hashimoto apply equally and are incorporated here. The Office Action relies upon Gohr for allegedly disclosing that S100 proteins are present in aging articular chondrocytes and S100 is a tTgase substrate in these cells. However, Gohr is absolutely silent with regard to using A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification in the cartilage matrix, as required by the claimed invention.

Accordingly, even if one were to combine Nurminskaya with Hashimoto and Gohr, the resulting combination would not be *prima facie* obvious over the claimed invention since the combined references do not disclose each and every claim limitation. Accordingly, withdrawal of the rejection is respectfully requested

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

No fee is deemed necessary with the filing of this paper. However, if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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